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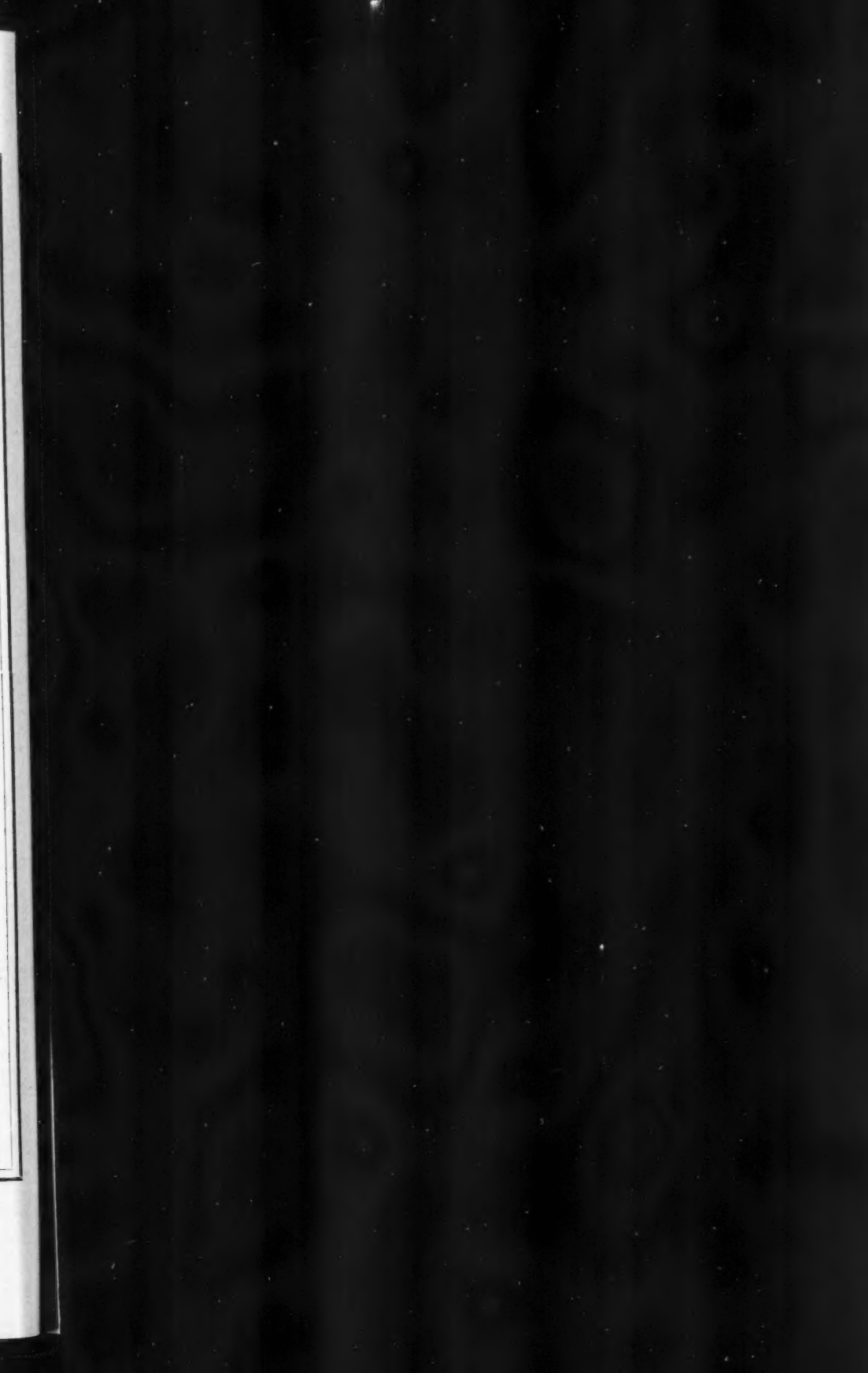

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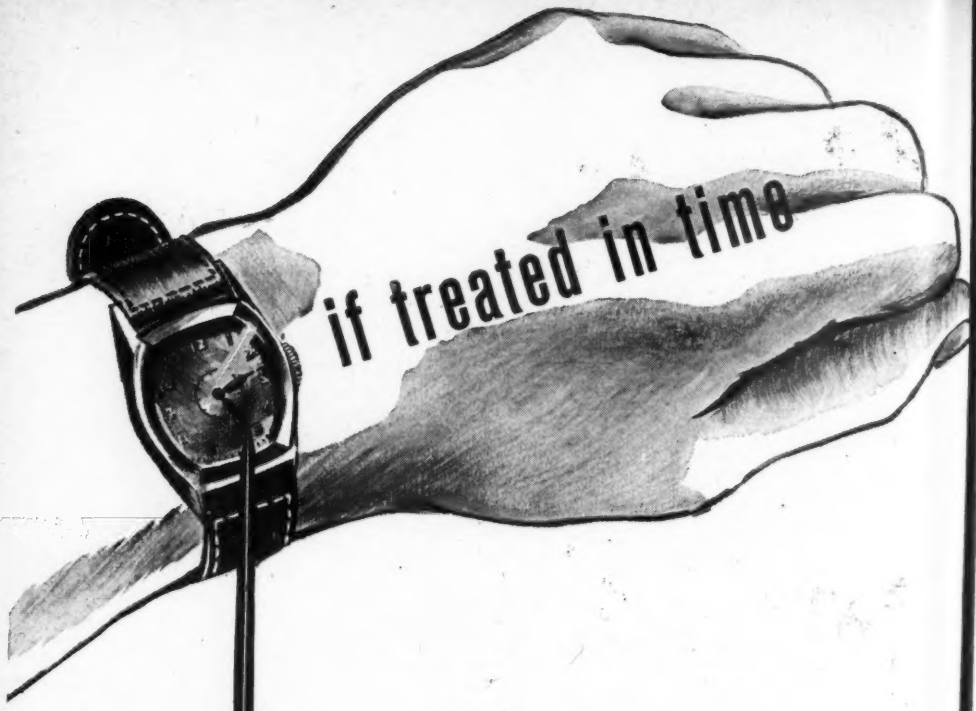

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EDITORIAL

MEDICINE IN POLITICS AND POLITICS IN MEDICINE *

By Ivor Griffith, D. Sc., F. R. S. A.

I PRESUME that one fact, and one fact only, entitled me to this opportunity to speak to you. Last year, for better or for worse, I was elected President of the American Pharmaceutical Association. Accordingly, it is as the coincidentally current President of that national group that I now address you. Manifestly, my statement shall be the recorded sentiment of that Association, and I give you now some data in that direction.

In 1938, at Minneapolis, the American Pharmaceutical Association adopted a series of resolutions on the subject of what was then loosely called the Wagner Social Security Bill, and which since has been changed in title and technique into the Wagner-Murray-Dingell Bill, S. 1161. These resolutions were clearly and naturally pointed into the channel regulating the distribution of drugs and in no wise indicated a frank opposition to the regimentation of medical practices and other health services so evident in the Bill. Here are the aforementioned resolutions:

> "RESOLVED, that the statement proposed by the Committee on Social and Economic Problems to indicate the present position of the A. Ph. A. on the subject of Socialization of Medical Services be approved and made public, as follows:
>
> WHEREAS, the distribution of drugs at state expense seems unnecessary and inconsistent except in cases which fall into the two following general categories: (1) unusually expensive drugs required to save lives of those unable to meet the cost because of income limitation; (2) drugs used in combating epidemics or diseases with serious social consequences, and

* Read before the meeting of the National Physicians Committee, held at the Waldorf-Astoria Hotel, New York, March 8, 1944.

WHEREAS, the cost of drugs in the treatment of routine or even serious ailments, unless continued over unusually long periods, is not catastrophic, and

WHEREAS, the need for withdrawing any considerable portion of the activity now exercised in the distribution of drugs and medicines from the recognized and legally regulated sources, namely, the pharmacies of the United States, is unnecesssary and may even be prejudicial to public convenience and welfare, be it

RESOLVED, that in the interest of the best type of health service, the principle of free choice of drugs by the physician within the limits of the official and otherwise approved materia medica, and free choice of pharmacist by the patient should prevail in any State or local system of supplying medical care at the complete or partial expense of the State."

However, in November, 1943, a new principle beyond these resolutions activated the Association to resolve in another direction, and I quote the more militant and more specific expression voiced by the Council of the Association:

"RESOLVED, that the Council of the A. Ph. A. go on record as being opposed to the attempted regimentation of medical practices and other health services and any autocratic principles contained in Title 9, Federal Medical Hospitalization and related benefits of the Wagner-Murray-Dingell Bill, S. 1161."

As spokesman for the American Pharmaceutical Association, this brief statement should suffice, and it may be that I stand in discourtesy when I essay to spread my personal opinions on the minutes of this distinguished gathering, but since I am on my feet, I have the presumption to by-pass the esthetic unities and, for a brief while, tell you precisely what is in my mind and heart.

No charitably-minded citizen can overlook the fact that there are many provisions in this bill which incline toward a new order. But the naiveté and novelty of the Bill, the cadginess and the coddlingness of it, the *"I am my brother's keeper"* gospel of it, are so acceptable, not just to the lame and the halt, but to the tame and the dolt, that opposition to any portion of it and on any score is *doubly* difficult. Therefore, such opposition must be *doubly* impelling, incisive, intelligent, and invincible. As such, it must reach legislators and representatives

by way of the people who elect them; a people who will have to be convinced on sound arguments that this cradle to the grave program is not compatible with our idea of American liberty.

Furthermore, the people should be reached *soon*. There is an election coming and we must remember that the political genius of the party in present power lies in appointment, not election. Perhaps we should remind ourselves and all others that we do have a voice in the choice of our politicians, and even of our President, so why not have a voice in the choice of our doctor? Is it possible that we shall some day be forced to think of our physician, or pharmacist, or dentist or nurse in terms of their political party? God forbid!

On the other hand, let us not be smug and so "holier than thou". The health professions must determine how their services to the people can and shall be improved, and no one denies that any service in our complex society is so good that it cannot show improvement. There *are* people in America who *are not* receiving adequate medical care!! These people as well as those in better social station are gradually being sold from within and from without the health professions that an overall health insurance *can* be provided and should be provided. But they should be given a practical plan of such insurance that definitely conserves private enterprise and keeps government where it belongs. I note the resolutions adopted by the National Physicians Committee in November 1943 and I quote from Section E: "Encourage and provide state or local financial aid rather than Federal subsidies to insure medical care for the indigent."

That resolution rings the bell with me, and it *should* with *every* citizen jealous of the American tradition, eager to uphold initiative and enterprise, and firm in the conviction that government HAS NO BUSINESS IN BUSINESS!!

I wonder whether one of the most recent utterances of that great and practical American Doctor of Economics, Mr. Bernard M. Baruch, might not be a most fitting quotation for insertion at this point. Thus spoke Baruch in a recent statement given to a Philadelphia newspaper:

> "Surely it must be manifest to all Americans that if at the end of the war, we are to place America on the high road to prosperity we must get Government out of business and give business a free, unhampered hand."

"Simple, sound, and sensible" was the newspaper's comment on Mr. Baruch's report.

Thomas A. Edison discovered electric light in more ways than one and there is illumination, power, and perpetual currency in this quotation from his writings, "There is far more danger in public monopoly than there is in private monopoly for when the government goes into business, it can always shift its losses to the taxpayers. The government never *really* goes into business for it never makes ends meet and that is the *first* requisite of business. It just mixes a little business with a lot of politics and no one ever gets a chance to find out what is actually going on,"—and so another Edisonian gift to posterity.

That most famous sign-painter and aphorist of modern history, Winston Churchill, who can compress bundles of thought into a terse and pointed phraseology, states, "We must beware of trying to build a society in which nobody counts for anything except a politician or official; a society where enterprise gains no reward and thrift, no privileges."

After uttering so starkly truthful a statement as the foregoing, I can scarcely understand how Mr. Churchill stands in so well with what is still called the New Deal. War, of course, justifies as practical, much of the centralization of authority in agents and agencies of the government. Thank God, however, that in the long range program of a democracy, war can *only* be considered as a necessary evil to be extirpated as rapidly as possible by Victory. But many opportunists in and out of Government use the war period for purposes which peacetime could *never* tolerate.

Today, with our land at war, who contradicts or countervails the theories and practices of existing government with rebellious reactions is regarded by some as not being in the American spirit. When we make non-conforming utterances, even though levelheadedly, we are charged with being spectacular and with using the spotlight when we should be using the X-ray. Yet, it may be that the barking of Barkley has awakened all of us to thinking and acting. This bill which now finds me heretic in opposition is beautifully decorated in order to appeal to the man on the street, but fundamentally it is only further evidence of the fact that the American citizen is to have his liberty whittled away, chip by chip, and its design is to regiment every citizen all the way from the episode to the epitaph. Therefore, although I speak in generalities, I insist that insofar as many provisions of this bill suppress free enterprise and by-pass the God-given privilege of free choice, then I am against it.

At another meeting of this group, I listened to an address by Mr. Raymond Moley. I had heard the address, or one like it, and so during regurgitations in the speech, I turned to the Muse for comfort and on the back of my ornate menu, the Muse laid this graphitic egg and I give it to you, hard-boiled, whether you want it or not. There was so much talk of the four freedoms and I remembered while listening, how the little yellow canary at my home enjoyed every one of the much-touted four freedoms, and yet missed, even from a bird's-eye-view of life, the greatest possession of all, namely, *Liberty,* and so I terminate these remarks with an alleged poem, "The Song of the Canary",

I worship God and pour my song
Upon His praise, the whole day long.
There's none to tell me what to trill,
I run my cadences at will;
For food I never have to search,
No danger haunts my eerie perch.
Secure in this, my gilded cage
The full four freedoms I engage.

But Ah! my friends, and Oh! my friends,
With just these four, my freedom ends,
The God that gave me right to sing
Gave me as well—the gift of wing.
Open my cage door—Watch me fly
Up to my own belonging sky.
What can the freedoms mean to me
Unless I have my liberty?

(I. G.)

DETECTION OF TUBERCLE BACILLI IN SUSPECTED ENVIRONMENTS

By Ralph Pressman, Ph. D.*

IN an attempt to determine the tuberculocidal efficacy of a carbon-arc lamp on an air environment it was necessary to ascertain first, quantitatively, if possible, the existance of tubercle bacilli in such environment.

Pressman (15) suggested a new method for the collection and treatment of air and dust for isolating, in pure culture, tubercle bacilli. While this method was an improvement over former techniques it left much to be desired. Two inherent disadvantages were noted: first, the large number of contaminations, varying, of course, with the cleanliness of the environment sampled; and second, the unreliability of oxalic acid as a specific suppressant for contaminating microorganisms. The term suppressant in this paper indicates any chemical that is used to kill or retard the growth of all microorganisms other than the tubercle bacillus. Accordingly an attempt was made to overcome these disadvantages and also to introduce more reliable methods.

Corper and Uyei (5) made a comparative study of chemicals which are used to suppress contaminants and concluded that oxalic acid in a concentration of 5 per cent was most efficient. In their work they were primarily concerned with the treatment of sputum and other body fluids in which the bacterial flora is generally about the same. There are but scanty data in the literature on the treatment of inorganic material, as is found in dust, for the concentration of tubercle bacilli or for the suppression of contaminating organisms.

Materials and Methods

Experiment I

(1) *Suppressants used:*

(a) Oxalic acid ($C_2H_2O_4 \cdot 2\ H_2O$), 5 grams in 100 cc. of distilled water.

* Department of Bacteriology, Philadelphia College of Pharmacy and Science.

(b) Sulfuric acid (H_2SO_4), 6 per cent standardized solution.

(c) Sodium Hydroxide (NaOH), 3 per cent standardized solution.

(2) Normal Horse Serum, without preservative.

(3) Lowenstein's modified medium, described below.

Collection of material—Several sterile porcelain evaporating dishes, 60 cc. capacity, were filled with sterile isotonic salt solution and placed on the floor of the room to be sampled. After exposure for one week, the contents were transferred to a sterile flask.

Series A—Fifty cc. of dust suspension were transferred to each of four sterile centrifuge tubes and centrifugalized for 10 minutes at 1800 r. p. m. The supernatant portions were aspirated, leaving 1 cc. of sediment in each tube. One cc. of the respective suppressant was added to each of the sediments. The mixtures were shaken and incubated in a water bath at 37° C. for 30 minutes. After incubation, a predetermined amount of acid or alkali was added to the sediment. One-half cc. of the neutralized mixture was seeded, in duplicate, on Lowenstein's modified medium and placed in the incubator at 37° C.

Series B—One cc. of sterile horse serum and 2 cc. of the respective suppressants were added to the 1 cc. of sediment obtained after centrifugalization. The subsequent treatment was identical to that in Series A.

Animal inoculations—The remaining neutralized mixtures of all the tubes in both series were pooled. Three cc. of the pooled mixture were injected subcutaneously into each of two guinea pigs, in the region of the left groin.

Findings

Series A	*Series B*
Negative	Positive when using 3 per cent sodium hydroxide.
	Negative when using other suppressants.

Animals—Forty days after injection, 0.1 cc. O. T. (1:10) was injected intradermally. Within 48 hours there was an area of redness

and edœma measuring 23 x 17 x 1.5 mm. Two weeks later a second tuberculin injection produced a positive reaction of plus 2 (+ +). The area measured 16 x 16 x 1.5 mm. Five days later an autopsy was performed, as the animal was found to be pregnant. Focal necrosis was found in the liver. The tracheobronchial lymph nodes were very much enlarged but definite caseous foci were not found. All the other organs were normal. Acid-fast bacilli were demonstrated in the tracheobronchial lymph nodes upon staining.

Another guinea pig treated as above gave negative tuberculin reactions and the findings at autopsy were negative.

Experiment II

In this experiment 10 cc. of dust suspension were used instead of 50 cc. as used in Experiment I. The procedure in every other respect was identical to that above. All findings (cultures and animal inoculations) were negative.

It will be noted from the above experiments that the chances for isolating tubercle bacilli are greater when using a larger volume of material. It was pointed out by Pressman (15) that the mucopurulent material surrounding the tubercle bacilli in a sample of sputum may serve as a buffering or protective agent against the detrimental action of the chemicals used. This seems to be borne out by Experiment I, Series B. Experiment II seems to indicate what has been mentioned before (15), that if tubercle bacilli are present in the air and dust they are present in relatively small numbers. It is safe to assume, also, that a number of them are dead or at least attenuated.

The absence of growth in most of the cultures in the above experiments suggested the possibility of a tuberculocidal action on the part of the chemicals used. In the following experiment an attempt was made to determine quantitatively the relative number of bacilli killed due to treatment with the chemicals used above.

Lurie (14) encountered difficulty in obtaining constant colony counts on ordinary egg medium. He compared the number of colonies obtained from seeding a given amount of infected tissue on Dorset's, Petroff's and Lowenstein's media with that obtained on Lowenstein's medium in which bone marrow infusion replaced the distilled water required by the formula (12). He found that from 100 to 200 per cent more colonies of tubercle bacilli developed on the

modified Lowenstein's medium. This medium, with Malachite green substituted for Congo red, in 0.034 per cent concentration, to suppress contaminants, was used in these experiments.

Experiment III

A suspension of Ravenal S was made so that 1 mg. was contained in 1 cc. Decimal dilutions were made and plated. A concentration of 0.0001 mg. per cc., equivalent to 200,000 bacilli per cc., was used in this experiment.

The method of treatment was identical to that used in Experiments I and II, Series A and B. The findings of this experiment are given in Table 1.

TABLE 1

Showing the effect of suppressants on tubercle bacilli in the presence or absence of normal horse serum

Suppressant	Average number of bacilli per cc. before treatment	Average number of bacilli per cc. after treatment	
		In the presence of horse serum	In the absence of horse serum
5 per cent oxalic acid	200,000	1,300	0
6 per cent sulfuric acid	200,000	7,000	0
3 per cent sodium hydroxide	200,000	innumerable	innumerable

It is evident from the data in Table 1 that 5 per cent oxalic acid and 6 per cent sulfuric acid display a tuberculocidal effect on the bacilli. Three per cent sodium hydroxide had no apparent effect. In Experiment I, Series B, the only dust suspension showing growth was that treated with 3 per cent sodium hydroxide. In the presence of horse serum the effects of the acids were less marked indicating that an albuminous material may have a protecting effect on the tubercle bacillus. This may account for the apparently harmless effect on tubercle bacilli when these acids (5) are used for the concentration of bacilli in sputum and other body fluids.

Corper and Uyei (6) found a 3 per cent sodium hydroxide solution less efficacious than the above mentioned acids for contaminators

in tuberculous materials such as urine, sputum, and tissue. They also found (5) a virulent strain of the avian tubercle bacillus that proved highly resistant to all of the chemicals used. Their results indicated that specificity of some chemicals for some species might be used for differentiating the avian species from the human and bovine species.

Since the results of the above experiments indicated that a 3 per cent sodium hydroxide solution was less harmful than either of the acids employed, an attempt was made to determine the specificity of some commonly used chemicals on various species of tubercle bacillus and also on different strains of the same species.

Preliminary findings revealed that of six species studied, consisting of three human strains: H 37, A 10, and Gluckson (obtained from Dr. Corper); two bovine strains: Bovine C and Ravenal S; and one avian strain: Avian 12, none was harmed by 3 per cent sodium hydroxide whereas 6 per cent sulfuric acid killed all the species tested and 5 per cent oxalic acid killed 2 strains of human, Gluckson and A 10, as well as Bovine C.

The results obtained above with the commonly used chemicals for the suppression of contaminants suggested that a chemical the action of which could be checked after a definite time might be very desirable.

The literature abounds with reports on the germicidal properties of chlorine-containing compounds. Uhlenhuth and Xylander (20) first investigated the usefulness of antiformin, a hypochlorite, as a selective suppressant for undesirable contaminants in sputum and tissues.

Charlton and Levine (3) stressed the desirability of using a compound such as chloramine-T because of the state of purity in which chloramine-T may be obtained on the market and the ease with which the desired concentration may be duplicated. They pointed out that the efficiency of chloramine-T varies with temperature, reaction (pH) and concentration. Schmelkes and Horning (16) reported on the advantages of azochloramide (a new chlorine-containing compound) over chloramide-T in organic substrates.

Koch first achieved artificial cultivation of the tubercle bacillus upon blood serum. Since then a great variety of media have been suggested for the primary isolation of tubercle bacilli from body fluids or tissues. Schwabacher (17) made a comparative study of several

media and concluded that an egg-saline-glycerine medium was best. Lurie (14) pointed out that if bone marrow infusion is used to replace the water in Lowenstein's formula (12) the resultant product displays marked nutrient properties.

Since no reference is made anywhere regarding the isolation of tubercle bacilli from a suspension of dust, and since it might be more desirable if a large volume of dust were seeded, a medium had to be found capable of being used for primary isolation and one to which a large volume of sample could be added.

The desirability of using a large volume of dust suspension, using a chlorine-containing compound (the action of which could be checked upon the addition of an inert chemical, such as sodium sulfite) and the search for a suitable culture medium suggested the next experiment.

Preliminary experiments revealed that when 0.000,001 mg. of Ravenal S, suspended in 50 cc. of saline, was added to 100 cc. of Lowenstein's modified medium contained in a 500 cc. Erlenmeyer flask, growth was apparent in 27 days, whereas when a transfer of Ravenal S was made, from a stock suspension, on a slant of modified medium growth was apparent in 18 days.

Experiment IV

Chemicals used:

(1) Chloramine-T (Sodium paratoluene-sulfonchloramide), Eastman Kodak Company; assay, 12.4 per cent active chlorine.

(2) Azochloramide (N-N'-Dichloroazodicarbonamidine), Wallace & Tiernan Products, Inc.; assay, 0.01 per cent active chlorine.

Technique—The method used is essentially as follows: To a definite volume of dust suspension (20, 40, 50, 80 cc.), contained in a sterile beaker, there was added a solution of chloramine-T (or azochloramide) of such concentration to yield, in final solution, concentrations varying from 10 parts to 400 parts, of available chlorine per million. The mixture was shaken, then incubated for from 30 to 60 minutes at 37 C. After incubation a slight excess of sterile 5 per cent solution of sodium of sulfite was added. The sulfite treated mixture was shaken well, allowed to stand for a few minutes, and

then transferred to an Erlenmeyer flask containing Lowenstein's modified medium. The flasks were examined for gross contamination at the end of 5 days and then weekly after the third week. Incubation took place at 37° C.

It should be pointed out that prior to the actual experiments various combinations of eggs and potato starch flour were used in the Lowenstein modified medium in order to obtain a medium of such consistency that the dust suspension might more easily permeate the medium. After several tests it was found that the consistency of the medium had no apparent effect on the time necessary to observe macroscopic growth.

A summary of the results obtained with the 40 cc. volume of dust using chloramine-T is given in Table 2.

TABLE 2

Showing the relative efficiency of various concentrations of chloramine-T in suppressing contaminants in a suspension of dust.

Concentration chloramine-T As available Cl in p.p.m.	Total number of samples treated	Number of tubes showing contamination	Number of tubes showing no growth	Number of tubes showing positive growth
40	5	3	0	2
100	13	4	3	6
200	14	8	1	5
300	8	7	1	0

From the above table it will be seen that in a total of 40 tests, performed over a period of 14 months, and including 7 different series of experiments, no definite conclusions can be drawn as to the most desirable concentration to use. While it might seem that the highest concentration would be most efficient, the results obtained do not justify this conclusion. It would seem, rather, that the number of contaminations in a series of tests is dependent not only on the degree but also on the kind of contamination. These are factors that, for the present, are insurmountable.

It should be noted that chloramine-T in the dilutions used in the test apparently displayed no harmful effects on the controls. Azachloramide was found to be tuberculocidal in concentrations over 10 p.p.m.

Animal inoculations—The positive cultures obtained in these experiments were used for guinea pig inoculations. Approximately 8 cc. of saline were added to each of the flasks which were carefully rotated in an attempt to suspend the growth. (The water in the culture flasks had evaporated during incubation.) The washings were strained through sterile gauze, when necessary. Three cc. of the strained washings were injected intraperitoneally.

Findings: Tuberculin tests, unfortunately, were not performed on these animals.

Autopsy: No gross tuberculous lesions were observed. The inguinal lymph nodes were very much enlarged, and acid-fast bacilli were demonstrated in the latter.

Diagnosis: Positive tuberculosis.

There seem to be two possible explanations why typical lesions were not found in the guinea pigs: one may lie in the fact that a relatively very small amount of organisms was injected; the second and more plausible explanation may be that the tubercle bacilli may have lost some of their virulence.

An abundance of literature (19) has appeared in the last decade reporting the apparent difficulty when attempts are made to produce typical lesions while working with small amounts of suspected material. Others (19, 7) suggest examining the inguinal lymph glands as well as other lymph glands microscopically.

In view of the positive cultures, the enlarged inguinal nodes and the demonstration of acid fast bacilli in the nodes, a positive diagnosis is justified.

Despite the encouraging results obtained by exposing dishes to the air and dust for seven days, it would seem that only a small proportion of the tubercle bacilli actually present in the air of a tuberculous environment eventually reach the dishes.

Wells and Wells (21) in an excellent study on air-borne infection, particularly respiratory infections other than tuberculosis, pointed out that droplets expelled into the air from the nose and throat in sneezing, coughing, and the like, do not necessarily fall to the ground as was suggested by Flugge. As droplets become smaller, the surface exposed to air resistance becomes relatively greater and droplets fall more and more slowly as the size becomes progressively smaller. The rate of evaporation, which also depends on the surface

area, becomes relatively more rapid as the droplet volume becomes smaller. Some size must exist below which a droplet could not fall the height of a man without complete evaporation. This droplet size has been estimated as approximately 0.1 mm. in diameter.

Transmission of infection through the air may therefore take one of two forms, depending on the size of the infected droplet. The more obvious form is droplet infection proper. It applies to droplets larger than 0.1 mm. in diameter which are rapidly removed from the air by gravity before they can dry and within a short distance from the source. The second form may be called air-borne infection and deals with the dried residues of infected droplets, or droplet nuclei, derived directly from droplets less than 0.1 mm. in diameter. Droplet infection may change into air-borne infection when larger drops settle, evaporate and are lifted into the air as dust. The time interval between the settling out of the larger droplets and their subsequent evaporation, when they are lifted into the air as dust, is relatively long and an uncertain one.

The dish method of Pressman (15) may be criticised on the following points: (1) that the dishes were placed on the floor in each corner of the room to be sampled, and since a current of air may raise some of the particles of dust high enough to fall into the dish, such particles are not, as yet, potentially infectious; (2) the tubercle bacilli found in the dishes are no indication of the number that may be suspended in the air; and (3) if, as it is assumed, droplets larger than 0.1 mm. in diameter dry and are raised as dust in one day and all the tubercle bacilli fall into the dishes on that day, it will then be 8 days before they are treated and cultured.

Cadeac (2) reported that he was unable to reduce sputum to dust until it had been dried ten to twelve days, while the tubercle bacilli had been nearly vitiated on the sixth day. Sticher (18) and Beninde (1) found it difficult to demonstrate living bacilli in dried and pulverized sputum under natural conditions.

Pressman (15) in addition to using the dish method also used the Wells centrifuge. Since he permitted the centrifuge to run for only 20 minutes, aspirating about 25 cubic feet of air, it is not surprising that he failed to obtain positive results.

It will be seen, then, that there are several distinct factors inherent in the above review: the criticism of the dish method, the effect of exposure on tubercle bacilli, and the fact that the operation of the Wells centrifuge for 20 minutes was not long enough to be consistent

with a true representation of the bacterial flora present. In view of these facts it was felt that if the Wells centrifuge were allowed to run continuously for about three hours, results more consistent with the true condition of the environment might be obtained. In a test such as this, the air *per se* is tested rather than the dust, although the dust raised at the time the centrifuge is being run might also be included in the sample.

Experiment V

Suppressants used:

(1) Oxalic acid, (2) sulfuric acid, (3) sodium hydroxide, (4) chloramine-T, (5) azochloramide.

Sampling:

The air of the fluoroscopic room at a large institution was aspirated for three hours during a clinic. There were at least three people in the room at the time of sampling.

Technique—Twenty cc. of sterile saline were placed into a sterile Wells tube, inserted in the centrifuge head, and the machine was started immediately. After three hours the tube was found to be dry; a mixture of salt and dust lined the wall of the tube. Twenty-five cc. of sterile distilled water were added to the Wells tube and with careful rotation the residue was suspended and allowed to flow to the bottom of the tube.

The method of treatment was essentially that of Corper and Uyei (5). One cc. of the mixture, which was rather dirty, was placed in each of six graduated centrifuge tubes. To each of these tubes was added respectively 1 cc. of the following suppressants: 5 per cent oxalic acid, 6 per cent sulfuric acid, 3 per cent sodium hydroxide, chloramine-T 200 p.p.m. in final dilution, azochloramide 100 p.p.m. in final dilution and sterile distilled water. The tubes were shaken well, placed in the incubator at 37° C. for 30 minutes, after which 8 cc. of saline were added. After centrifugalization, cultures of the sediment were made on Lowenstein's modified medium. This experiment was repeated twice a week, Tuesday and Thursday, for four consecutive weeks.

Findings—Of 40 treated tubes which were seeded subsequently on Lowenstein's modified medium, 30 (or 75 per cent) showed con-

tamination within 4 to 6 days. It is interesting to note that of 10 tubes showing no growth, 8 were treated with 6 per cent sulfuric acid and 2 were treated with 5 per cent oxalic acid.

Here again it will be seen that too much reliance cannot be placed on the suppressants. Where there was no contamination there was also no growth. Indeed the suppressants cannot be considered innocuous. It should again be pointed out that the degree of contamination will always play an important role in such experiments.

Animal inoculations—In order to determine whether or not tubercle bacilli were actually present in the room being sampled and to determine whether a series of frequent small dose injections, simulating, in a sense, frequent contacts of humans, will cause tuberculosis in guinea pigs, a number of guinea pigs were injected with the untreated dust suspension.

As previously mentioned, the salt-dust residue in the tube in the Wells centrifuge was suspended with 25 cc. of sterile distilled water, and after mixing 6 cc. were used to inject guinea pigs.

Three cc. of dust suspension were injected into each of six guinea pigs. The injections were made twice weekly, for four consecutive weeks, subcutaneously in the inguinal region, alternating the site of injection from the left to the right side. In all, eight injections, of 3 cc. each were made into each of 6 guinea pigs.

Findings—The guinea pigs were tuberculin tested every month. At the end of the third month although negative to the tuberculin test, a few guinea pigs displayed a marked loss in weight. All the animals were sacrificed at the end of the fourth month. Autopsy showed no evidence of tuberculosis.

In Experiment V, using the Wells centrifuge, it was mentioned that the tube in the centrifuge, after three hours' centrifugalization, was found to be dry. Wells (*22*), in his studies found that the Wells tube, containing 20 cc. of water, was dry in about one hour. Since only about 60 cubic feet would be aspirated in so short a time, and since what dust may have clung to the wall of the tube was diluted to 25 cc., it appears that the injections, made into guinea pigs, may have contained too few bacilli to produce positive results. When the Wells tube is dry with nothing to take up the dust particles there should be merely an exchange of air within the tube. It became obvious that some substance would have to be added to the Wells tube which would not be evaporated to complete dryness

and yet which would take up or hold back the dust particles. If 20 cc. of a 10 per cent glycerin were used the water would be entirely driven off in the process of centrifugalization but the glycerin would form a thin layer on the inside wall of the Wells tube which should prove adequate in taking up the dust particles. Here was a method for collecting and concentrating the material at one and the same time.

In a preliminary study it was found that glycerin displayed no harmful effect on the tubercle bacillus. Accordingly the following was performed.

Experiment VI

The method is essentially that described in Experiment V, except that 20 cc. of 10 per cent glycerin replaced the saline. The centrifuge was allowed to run for 6 hours continuously, during and after clinic. To the small amount of glycerin-dust mixture clinging to the inside wall of the Wells tube two cc. of sterile distilled water were added. With a nipple at the end of a sterile pipette, the inside of the tube was washed several times and the contents withdrawn and placed in a sterile graduated tube. Rinsing was repeated until the volume was made up to 4 cc. Chloramine-T, being the most promising suppressant, was used in this experiment.

To the 4 cc. of glycerin-dust mixture was added 1 cc. of chloramine-T of such concentration as to yield in the final dilution 200 p.p.m. of available chlorine. The tube was shaken and placed in the incubator at 37° C. At the end of 30 minutes, 0.75 cc. was withdrawn and placed in a serological test tube which contained an excess of sterile sodium sulfite. After thorough mixing the contents were transferred to a tube of Lowenstein's modified medium. The dust suspension was returned to the incubator and at 30 minute intervals 0.75 cc. was withdrawn and treated as above. The total time of exposure to chloramine-T was three hours.

As a control 1 cc. of a dilute suspension of Ravenal S, containing 0.000,001 mg., was treated as above by adding to it 1 cc. of dust suspension, 2 cc. of glycerin and 1 cc. of chloramine-T. Incubation was at 37° C.

Findings: Of six exposures to chloramine-T, ranging from 30 to 180 minutes, 4 tubes showed contamination; in the other two there was no growth. Similar findings were noted in the control

tubes. Again it will be seen that the kind and degree of contamination is an all important factor. It is evident that when the chemical used has the faculty of suppressing the contaminant it may also display a deleterious effect on the tubercle bacillus. Results of further studies on selective suppressants will be reported later.

Exposure Experiments

Lurie (13) in a comprehensive study on air-borne infection, and others (10, 11) whose work preceded that of Lurie, showed that aerial infection plays the more important role in the spread of tuberculosis. While their work (10, 11, 13) should become a milestone in establishing definitely the significance of air-borne infection in so far as tuberculosis is concerned, it is nevertheless true that most of the work has been confined to animals which were exposed in cages in the same room with experimentally infected animals. Sight, however, should not be lost of the fact that the conditions of human exposure are not, by any stretch of imagination, comparable to those met in the animal experiments.

For the sake of completeness it was felt that animal exposure experiments should be included, particularly in those rooms where positive results were obtained by some of the methods described above.

Twelve guinea pigs were distributed among three waiting rooms of a tuberculosis clinic. Three animals were placed in each of four cages. At the end of the nineteenth month two of the animals showed a positive tuberculin reaction. At the end of the twentieth month a third animal showed a positive reaction. At the end of the twenty-first month the animals were sacrificed. Only one of the animals proved to be positive. Autopsy revealed the following findings: In the upper left lung on the underside there was a grey nodule in which was one minute area of opaque tissue. The entire nodule measured about one mm. across. The remainder of both lungs showed no abnormalities except for a slight anthracosis. The tracheobronchial lymph nodes on the left side were enlarged. Several acid-fast rods were demonstrated in the tracheobronchial lymph nodes.

It has been shown above that the possibility of isolating tubercle bacilli from dust is greater when a large volume of dust is used. The method employed above makes use of a bulk of dust suspension which

beside being unwieldy requires large Erlenmeyer flasks, in addition to unusually large amounts of Lowenstein's modified medium.

If a large volume of dust suspension could be reduced to a smaller bulk without having any deleterious effects on the tubercle bacilli such change would make the method more practicable.

Flosdorf and Mudd (8) have described an apparatus for the preservation of labile biological materials. The procedure is one of rapid freezing at a very low temperature and rapid dehydration from the frozen state under high vacuum. The term "lyophile" was originally applied to serum so treated. Recently they (8) have suggested the word "cryochem" to denote desiccation *in vacuo* from the frozen state by means of chemicals.

Henderson (9) has reported that in the process of concentration of tuberculous material no deleterious effects were noted on the tubercle bacillus. Here, then, was a method for concentrating quite a large volume of dust suspension, taking up the residue and treating or injecting this concentrate. Accordingly, the following study was undertaken.

Experiment VII

Suppressants—Same as used in Experiment V.

Collection of materials—Sterile porcelain evaporating dishes, of 60 cc. capacity, were filled with sterile saline and placed on the floor in the corners of the men's waiting rooms for one week. The contents of the dishes were collected in a large Erlenmeyer flask. The total volume of dust suspension was 1800 cc. which was divided into two equal parts. One part was to be used as a control to determine the effects of "lyophilizing" on the tubercle bacillus.

After thorough mixing, 75 cc. of dust suspension were transferred by means of a sterile graduated cylinder to each of 8 twelve-ounce bottles and evacuated over a period of six days.

Treatment. Series A—Four cc. of sterile distilled water were added to each of 4 bottles, which were lined with a thin spongy and porous layer of salt and dust. By careful rotation most of the residue was suspended. The contents were transferred to a sterile flask. Two cc. more of the distilled water were added to the bottle for a final rinsing and then added to the original washings.

To 3 cc. of concentrate an equal volume of suppressant was added, the tubes shaken, placed in the incubator at 37° C. for 30

minutes after which a predetermined amount of alkali, acid, or sodium sulfite was added to the treated concentrates. One-half cc. of neutralized mixture was seeded, in duplicate, on Lowenstein's modified medium.

Series B—In this series the dust residue was suspended in 50 per cent sterile horse serum (in sterile distilled water). The method of treatment was identical to that in Series A.

Controls—To the second flask of 900 cc. of dust suspension was added 1 cc. of a suspension of Ravenal S, equivalent to 0.000,001 mg. The method of distribution, evacuation and treatment was identical to that in Series A and B above.

Animal inoculations—The dust suspensions remaining, after 3 cc. were used for treatment prior to culturing, were used for guinea-pig injections. Ten guinea pigs in all were injected, 4 of which were injected with untreated suspension while 6 guinea pigs were injected with chemically treated suspensions.

Findings: All but two animals died within 24 hours. It is safe to assume that the toxic effect of the dust *per se* was responsible for death in the case of the untreated concentrate, while in the treated concentrate there was a relatively high concentration of salt resulting from acid-base neutralization, in addition to the toxic effects of the dust *per se.*

The two guinea pigs which lived were sacrificed after ten weeks. Autopsy revealed generalized tuberculosis in both.

Cultures—All of the tubes seeded with dust suspension were sterile after 6 weeks' incubation. In the case of the controls those tubes which were treated with 3 per cent sodium hydroxide showed typical growth. Staining revealed acid-fast bacilli.

All the other tubes were uniformly sterile. Here as above it will be noted that the chemicals used in these experiments are not reliable.

Summary and Conclusions

In an attempt to find a reliable method to demonstrate the presence of tubercle bacilli in an environment so as to determine subsequently the tuberculocidal properties of a carbon arc lamp several experiments were conducted.

From the results obtained one is led to conclude that no single method of collection and treatment of dust or air will serve. The greatest deterring factor is the variability of the environment sampled. This, for the present, is the one insurmountable obstacle.

The results obtained from these experiments are, however, in themselves significant.

1. It was found that a large bulk of dust suspension offers a greater possibility of obtaining positive results than might be obtained when using a small sample. This indicates, as has been pointed out before, that the number of viable tubercle bacilli in a tuberculous environment are relatively few.

2. Albuminous material enveloping the tubercle bacillus in body fluids serves as a protective when chemicals are used to concentrate such fluids prior to culturing or inoculation into animals.

3. Lowenstein's bone marrow infusion medium was found to possess the property of supporting primary growth when large volumes, 40 cc. or more, of treated dust suspension were seeded on it.

4. A chlorine-containing compound, such as chloramine-T, has been used with a certain amount of success. It was found to be more satisfactory than other commonly used chemical suppressants in that its activity can be checked by the addition of an inert chemical.

5. The Wells centrifuge, using 10 per cent glycerin as a collecting medium, running for 6 hours and aspirating approximately 360 cubic feet of air, yielded no conclusive results. In this apparatus we have a method that should make sampling of air relatively simple.

6. As an alternative method, and one particularly suitable for sampling a large bulk of dust, collected over a period of a week, the "cryochem" apparatus would serve very well if the tubercle bacilli could be separated from the bulk of dust.

In the process of dehydration no apparent ill effects were noted on tubercle bacilli.

7. When guinea pigs are injected twice a week over a period of four weeks with small amounts of dust, simulating, in a sense, frequent contacts of humans, negative results were obtained. It is felt that if more concentrated samples were used the results might be more promising.

8. Guinea pigs exposed in the waiting room of a tuberculosis clinic displayed positive findings after 21 months of exposure. These results are in harmony with the findings of Lurie and others and stress again the potential dangers of air-borne infection.

REFERENCES

1. Beninde, M.: *Ztschr. f. Hyg. u. Infektnskr., 30*:193 (1899).
2. Cadeac, M.: *Lyon Med., 105*:893 (1905); *ibid., 111*:532 (1908).
3. Charlton, D. B., and Levine, M.: *Jour. Bact., 30*:163 (1935).
4. Corper, H. J.: *J. A. M. A., 91*:371 (1928).
5. Corper, H. J., and Uyei, N.: *Jour. Lab. & Clin. Med., 13*:469 (1928); *15*:348 (1930).
6. Corper, H. J., and Uyei, N.: *Amer. Rev. Tuberc., 16*:299 (1927); *9*:115 (1927).
7. Costigan, S. M.: *Jour. Bact., 32*:57 (1936).
8. Flosdorf, E. W., and Mudd, S.: *Jour. Immunol., 29*:389 (1935); *34*:469 (1938).
9. Henderson, H. J.: Personal communication.
10. Lange, B.: *Zeitschr. f. Hyg., 103*:1 (1924).
11. Lange, B., and Nowoselsky, W.: *Zeitschr. f. Hyg., 104*:286 (1925).
12. Lowenstein, E.: *Deutsch. med. Woch., 56*:1010 (1930).
13. Lurie, M. B.: *Jour. Exper. Med., 51*:743 (1930); *51*:753 (1930); *51*:769 (1930); *58*:305 (1933).
14. Lurie, M. B.: *Jour. Exper. Med., 60*:164 (1934).
15. Pressman, R.: *Amer. Rev. Tuberc., 35*:815 (1937).
16. Schmelkes, F. C., and Horning, E. S.: *Jour. Bact., 29*:323 (1935).
17. Schwabacher, H.: *Tuberc., 18*:199 (1937).
18. Sticher, R.: *Ztschr. f. Hyg. u. Infektnskr., 30*:163 (1899).
19. Topley, W. W. C., and Wilson, G. S.: "The Principles of Bacteriology and Immunity," William Wood & Co., Baltimore, 1934, pp. 2, 821.
20. Uhlenhuth and Xylander: *Berl. klin. Wchnschr., 45*:1346 (1908).
21. Wells, W. F., and Wells, M. W.: *J. A. M. A., 107*:1698 (1936); *107*:1805 (1936).
22. Wells, W. F.: Personal communication.

NEW DEVELOPMENTS IN PHARMACEUTICAL PRACTICE*

By Madeline Oxford Holland, D. Sc.

WITHIN the past ten years many striking changes have taken place in pharmaceutical practice. Principally, these changes have had to do with refinement of dispensing technic and with improvement in medicinal products. In fact, it is now evident that medical practice and pharmaceutical service have shown greater changes in these past few years than had been witnessed in any century-long period in the history of therapeutics. The only similar epoch-making developments of comparable nature were the establishment of rationalized botanical medication by Galen, in the second century, and the inception of chemical therapy by Paracelsus thirteen hundred years later. Just as the progress of mankind has been marked by successive periods of basic change, such as the "Bronze Age", the "Iron Age", and currently, "The Age of Plastics", so in Pharmacy we have seen similar evolution. As far as medical practice is concerned, we may now consider that we are in "The Age of Organic Synthetics."

Economic effect

It would not be proper, in this discussion, to devote more than passing reference to the economic changes which have been cause and effect with the trends in the science of therapeutics through recent decades. The problem has been materially intensified by the growing use of specific therapeutic agents. The change in prescription writing proclivity of the average physician reflects this transition of the pharmaceutical industry from the production of standard pharmaceuticals and galenicals to the development and promotion of organic specialties.

At the close of the last century, the pharmaceutical industry had grown to the point where it assumed the major proportion of the former manufacturing activities of the pharmacist. At the same time, the discovery of alkaloids opened the realm of active principles. The

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industry, of course, has carried this specialization a step further. The emphasis in modern therapeutics is increasingly on derived active principles, or their synthetic substitutes. We have seen within a space of a few years the discovery and development of what were entirely new groups of therapeutic agents. Among these were the vitamins, the hormones, the sulfonamides, and similar new and potent substances, all of which are basically complex synthetic organic chemicals.

Chemotherapeutic rationale

The rationality of such specific chemotherapy is obvious and the medical profession has adopted it to an increasing extent. Since the practice of the pharmacist depends in large measure on his medical colleagues, it is obvious that as a result the compounding and dispensing of drugs has been radically altered.

The increase in the volume of parenteral medication has also been noteworthy although pharmacists know that in nearly every instance, oral and topical application of medicaments is preferable to injectable medication both from the standpoint of patient preference, and as well from lesser cost. However, parenteral administration is of value in emergencies and it will always be a desirable method of administration.

Change in practice

The change in type of therapeutic agent, together with the promotion of these products as specialties by the industry, have done much to cause the medical profession to change its practice. To Pharmacy, therefore, is presented a challenge. It must recognize the need for a change in its role in the public health field, even though this change is to only a minor extent.

Pharmacy as a profession still controls the discovery, development, standardization, production and distribution of these new agents. We must, nevertheless, appreciate the present and probable future function of the various phases of the profession. The manufacturing aspect of the pharmacist has become a specialized function. The role of the dispensing and compounding pharmacist has likewise changed. While the latter may be called upon in the future to a lesser extent, to employ specific manipulation of ingredients on polypharmacal prescription, yet he faces a greater opportunity for professional service than ever before.

Three-fold duty

The professional prescription and hospital pharmacist of today has a three-fold duty. The first demand is for the formulation and perfection of more elegant pharmaceuticals. In this respect, the combination of therapeutic agents into the form of preparations is the responsibility and the opportunity of the pharmacist. Certainly the professional pharmacist has the requisite background of knowledge and experience which fits him for the development of newer and better formulas. For instance, the preparation of parenteral solutions, with due regard for sterility, potency and pyrogen-free state, is within the province of any good pharmacist. The dispensing of isotonic and buffered medicaments, the manufacture of fluids and ointments, and the preparation of tablets are fields that are open to the dispenser as much as to industry. With his basic knowledge kept up-to-date; with a minimum of equipment; and most important of all with the desire to do the work, the pharmacist is admirably equipped. The advantage held by the pharmacist in practice is that his is a much more flexible position. Because of his adaptability, he is able to present to his physician friends preparations representing new developments in medications, months before they reach the market as an industrial product. Naturally enough, he is not in a position to develop new endocrine products, or perhaps a new anesthetic, yet there still remains a great field of preparations and dosage forms which are his opportunity if he is willing to expend the effort.

The second challenge to today's pharmacist is in the wise and careful distribution of medicinals. Through the use and economical distribution of a new dangerous or potent drug, the pharmacist protects the welfare of his community. To say that he should have available at all times all of the newer agents may sound trite. Yet, even under today's improved economic status, the inventory of medicinal agents among drug stores or hospital pharmacies is by no means adequate. Equally important is the duty which has been largely ignored by most pharmacists, that of controlling the distribution and use of proprietaries. Today's war-time scarcity of physicians is increasing self-medication. Possibly the post-war demand for socialized medicine may reverse this tendency.

Professional information

Most important of all of the three great fields of service is that of the provision of professional information to physicians. We know

only too well that the physician of today is marvelously trained in diagnosis, and in the fundamentals of treatment. He is well aware of the physiological and pharmacologic significance of the drugs employed in or on the human body. However, he is to a degree unaware of what drugs are and of how they may be applied.

Pharmacy is the science and art of the selection, compounding and use of drugs. Therefore, in our profession, we must make certain that we provide to the medical profession this important technical information, which in turn is our own special province. We have the principal role of keeping abreast of all changes in therapeutics. Pharmacy must provide to the physician wise, unbiased information and suggestions as to the most desirable therapeutic agents to be employed. The physician today is learning to refer to Pharmacy for his therapeutic knowledge. Whether this dependence is upon the detail representative of industry or upon the professional pharmacist depends entirely upon the adequacy of either or both.

New developments

Let us review for a moment some of these new developments in therapy and the newly discovered agents which have made possible the great advance in medical care of the past months.

Most dramatic among the newer agents developed for the welfare of mankind have been the chemotherapeutic sulfonamide and microbiotic agents. Among the former agents, two new medicinal chemicals deserve special mention. They promise to render obsolete the popular drugs of today, such as sulfathiazole and sulfadiazine.

Sulfamerazine

Sulfamerazine is the monomethyl derivative of sulfapyrimidine or in other words, methyl diazine. It is the close relative of the dimethyl compound, developed originally in England. Experimental and clinical evidence indicates that it is effective in the treatment of pneumococcic, meningococcic, hemolytic streptococcic and gonococcic infections. It is more rapidly and more completely absorbed from the gastrointestinal tract than sulfadiazine or sulfathiazole, and is excreted much more slowly. This permits the swifter attainment of a high therapeutic blood level, and insures its maintenance over a longer period of time. This results in more economical treatment.

Sulfapyrazine

One of the most promising of the new antibacterial sulfonamide agents is sulfapyrazine, recently released under the Food and Drug Act for general use. It has been developed as a result of researches conducted in the last year or so. The value of sulfapyrazine lies in its apparent quality of therapeutic value similar to sulfadiazine, against beta-hemolytic streptococci and pneumococci. Coupled with smaller dosage to obtain effective blood levels and lesser toxicity, it has an additional possibility in that it may be equally or more effective than sulfaguanidine and succinylsulfathiazole in bacillary dysentery. Chemically, this product is an isomer of sulfadiazine, where its superior qualities may be traced to a mere rearrangement of the nitrogens in the pyrimidine ring.

Diasone

The really newest chemotherapeutic agent is one recently announced named "diasone." It is most interesting because of its chemical structure and its therapeutic possibilities. When neoarsphenamine was developed, it was made as a sodium formaldehyde sulfoxylate derivative of arsphenamine, which improved on the latter greatly. Now pharmaceutical research has hooked two of these sulfoxylate groups to two modified sulfonamide radicals, to produce disodium formaldehyde sulfoxylate diaminodiphenylsulfone, or diasone. What makes this particularly significant is that experimental and clinical trial seems to promise that diasone is effective against tuberculosis.

There are many other instances, however, where the sulfonamides prove ineffective. Either the drugs themselves are inactivated by pus, serum or other natural inhibitors, or the infectious organisms develop a resistance.

The discovery of penicillin and gramicidin have made possible the solution of this great problem. The former is an able supplement to the sulfonamides and promises to be a major contribution to medical practice. In order to understand the relationship imagine a ruler, with a major microorganism disease at each inch mark. The sulfonamides represent a ribbon covering from one end to, let us say, the sixth inch mark. The sulfonamides discovered so far are effective against pneumonia, streptococcal and gonorrheal infections and many others. However, there are some spots in these first six inches on

the ruler where the drugs are not entirely effective. And there remain the last six inches! Included therein are osteomyelitis, bacterial endocarditis and others heretofore almost invariably fatal.

Penicillin, of which we'll have more to say, represents another ribbon on the ruler, blanketing the sulfonamide ribbon almost entirely in those spots where the latter was ineffective, and most important of all, it covers up to the ninth inch mark. Here were acute osteomyelitis, chronic gonorrhea, endocarditis, influenza and good results are being reported even in syphilis. But let us consider these microbiotic chemotherapeutic agents, made from bacterial or mold products.

Gramicidin and Tyrocidine

Gramicidin, the forerunner of penicillin, has its place in modern therapy. It is an organic chemical substance extracted from certain soil bacteria, probably Gram negative types, which interferes with the normal metabolism of Gram positive bacteria. Dubos, who initiated this research, applied the principle that pathogenic bacteria enrich the soil. He placed in the soil, suspensions of living streptococci and staphylococci with the hope that these would cause the development of a microbial flora which would have an antagonistic effect upon Gram positive cocci. A culture of a strain of *Bacillus brevis* was further isolated from the soil. This bacillus destroyed living Gram positive organisms *in vitro* and *in vivo*. At first it was believed that an enzyme was responsible. Later it was found to be due to a toxic substance produced by the bacillus. It has also been found to occur naturally in soil, cheese and sewage. Another fraction obtained is tyrocidine.

Gramicidin, unlike tyrocidine, is not a gross protoplasmic poison. Gramicidin has been used in treating local infections such as empyemas, bovine mastitis caused by group B streptococcus, sinusitis, bladder infections, stasis ulcers, conjunctivitis and others. It has been employed in various forms such as in isotonic glucose or glycerin solution emulsion with water or mixed with oil. It has also been used in admixture with tyrocidine or tyrothricin, the mother substance. On sensitive tissues gramicidin should be used alone as the other substances are too toxic.

Penicillin

Of the newest microbiotic chemotherapeutic agent, derived from media on which the common green mold is cultured, too much cannot

be said. It is still unknown to practicing pharmacists, except from the standpoint of informative articles which have appeared from time to time. A few salient points are presented here, in order to review its features.

Penicillin is at present an impure sodium salt of a substance isolated from media in which *Penicillium notatum* has been cultured under controlled, sterile conditions. It is only 20-40 per cent pure although pure crystalline penicillin has been isolated, but not in any appreciable quantity. No one has been able to determine its chemical structure although much ground work has been laid. The calcium salt is believed preferable to the present sodium salt. The potency is evaluated in Oxford units and as a pure salt represents 1650 units per mgm., future treatment will probably be on weight basis. Standards are being evolved by government agencies and soon it will be "official" in the U. S. P. Its synthesis is problematical but possible. It is valuable against a number of sulfonamide resistant infections, particularly osteomyelitis and chronic gonorrhea and has given promise against bacterial endocarditis and syphilis, as well as a number of other infections such as pneumonia, influenza, gas gangrene, etc.

It must be administered parenterally or topically and cannot be given orally as it is inactivated by gastric juices. It is questionable from the economic standpoint whether it will ever be employed against diseases now amenable to sulfonamide treatment.

Blood plasma and serum albumin

The use of human blood in the treatment of humans is of course not a new development. The first transfusion of blood was made in 1654 by Folli with animals. However, the value of blood constituents for treatment of shock and similar conditions has been the greatest single contribution to World War II. Blood plasma and serum albumin are these marvelous products.

Plasma is being used to a considerable extent, particularly in the treatment of the casualties of war. More than 4½ million units, each representing a pint of whole blood, will be supplied to the Armed Forces this year. Plasma is official in either the liquid, frozen or dried state. The dried plasma is much more advantageous on the battlefield, because it does not require special equipment to maintain its state. Of course, loss of blood through wounds may not entirely be treated with plasma, nor can anemias. Whole blood is required.

There are several processes for drying blood plasma. All involve rapid freezing in a bath consisting of dry ice in cellosolve or acetone but the final process of removing the water differs.

In the "lyophile" process the water vapor is removed under high vacuum and condensed as ice in condensers maintained at the temperature of solid carbon dioxide,—78° C. A pressure well under 0.2 mm. is maintained.

The "cryochem" process employs anhydrous calcium sulfate or "drierite", which acts as a desiccant and removes the water vapor. A later improvement on this process dries or regenerates the chemical in the same chamber where the material is dried. This process is recommended where plasma is being dried in small quantities.

The "desivac" process is ideal for large scale operations. The water vapor is removed from the high vacuum chamber by entraining in oil which is then centrifuged to remove the water and returned. This eliminates the chemical desiccant and condensation apparatus. A fourth method, the adtevac process, employs the absorption of the water vapor by silica gel.

Serum albumin is another blood substitute being successfully employed and preferred by the Navy. The albumin is removed from the plasma and purified. It is just as effective and possesses the same margin of safety as does the whole plasma or whole blood. The serum albumin is crystallized from the blood and then made into a solution of 30 per cent strength. Only 100 cc. of this solution are required to produce an osmotic effect equal to that produced by 500 cc. of human plasma.

Other promising factors which research is developing from the other fractions of blood plasma also give great promise.

Many other fields of therapy have been radically affected in the past few months. Among these fields are the analgesics, dermatological products, anti-malarials, vitamins and hormones.

Demerol

Demerol is a new synthetic analgesic, recently released on the market. Chemically, it is a methyl-phenyl-piperidine-carboxylic acid ethyl ester. In activity it is comparable to morphine in its analgesic powers but it is not so likely to cause addiction. It possesses antispasmodic properties similar to those of atropine. An added advantage is that it does not possess the constipating properties of morphine. It is believed that demerol will replace morphine in 90-95%

of the cases where an analgesic is required. Tolerance to demerol is similar to that of morphine but less permanent. When the drug is withdrawn symptoms of withdrawal are evidenced but they are less severe than those caused by morphine withdrawal.

Biodynes

In the past few years extensive but controversial studies on the subject of cellular metabolism have been carried on by Cincinnati's Institutum Divi Thomae. Various fractions were obtained from living cells, which fractions were observed to possess some control over cellular metabolism. These were named "biodynes", from the words bios (life) and dyne (force). It has been found possible to stimulate in normal cells, respiration, growth or glycolysis of cells simply by the addition of the specific biodyne fraction for the particular function. Production of biodynes in the tissues is increased by an injury to the cells. Remarkable results are stated to have been achieved in the treatment of burns with the biodynes. Less time is required for healing, sepsis is absent, there is no scarring and only a minimum of pain.

Biodynes are now available for use in burn therapy. The fact that the skin takes in oxygen and releases carbon dioxide, which respiration can be controlled by external application of Biodyne R or the Skin Respiratory Factor, is also being applied in cosmetics. Now marketed are the SRF night cream and SRF lotion. It is believed that the appearance and texture of the skin will be improved by the restoration of respiration to the skin. Each ounce of the products contains 2000 units of biodyne R. However, this whole subject is questionable at present.

Flavines

Also effective against skin infections and found of value in treating second degree burns and in preventing infection in wounds have been certain dyes, such as proflavine. The flavines or acridine dye derivatives are not new to medicine. They have been employed for many years as antiseptics, but fell into disuse through misapplication and because of other factors. Now they are again regaining favor.

Acriflavine and its precursor, proflavine, are not severely toxic to the body, are comparatively non-irritating, do not interfere too greatly with phagocytosis, and their action is not diminished by the

presence of serum. They are particularly effective against staphylococci.

Quinine substitutes

Everyone is well aware of the shortage of quinine. Various substitutes have been under development for many years. Some of these are totaquine, quinacrine, and pamaquine.

Totaquine U. S. P. is a mixture of alkaloids from the bark of *Cinchona succiruba* Pavon and other suitable species of cinchona. It contains not less than 7% and not more than 12% of anhydrous quinine. The dosage recommended is 10 gr. three times daily for 7 days. It is almost as effective in this dosage as is quinine.

Quinacrine hydrochloride, or atabrine, is an effective antimalarial, superior, *in some ways, to quinine.* Pamaquine naphthoate or plasmochin is also believed somewhat effective as an antimalarial. Both of these synthetics are official in the U. S. P.

The National Research Council has recommended an efficient routine of therapy employing some of the substitutes in combinations. However, atabrine and plasmochin should not be given concurrently, as they are toxic together.

Aluminum hydroxide

Aluminum hydroxide has long been used in the treatment of hyperacidity. Only in recent years, however, has it attained general use in the treatment of gastric and peptic ulcers. It has found favor because an alkalosis cannot possibly develop during its use. It does not disturb digestion nor does it change to any degree the normal pH of the digestive juices in the stomach and intestines. The highest concentration possible is 5 per cent. Pharmacists can well investigate the possibilities of this as a product for dispensing.

The vitamins represent the major new market for the average drug store. The ones of primary importance are, of course, the synthetic C and major B vitamins, and natural A and D. However, recent research indicates that the so-called "minor" vitamins, particularly those of the B complex, should attain great importance.

Biotin

Within the group of water-soluble factors in the vitamin B complex, there is to be found one substance which will gain a place of

increasing importance in human nutrition in the near future. This growth-promoting, acrodynia factor is designated as biotin. It is a factor now known to be important to the nutritional development of molds, yeast, bacteria, rats and chicks. Its significance in human metabolism is only guessed at today, but the future may show its increased use.

Inositol

Another of the minor B complex vitamins is the substance called inositol, or the mouse anti-alopecia factor. It is believed to be the basal nutrient for the growth and proper maintenance of animal hair, which brings in a relationship with pantothenic acid, and possibly a value in human therapy.

Vitamin P

Vitamin P, or citrin, is an oxidation-reduction enzyme from citrus peel. It exerts some beneficial effect upon the state of the capillaries, decreasing fragility and preventing localized hemorrhages. Some investigators have found it valuable in hemorrhagic purpura in which increased capillary resistance results when it is administered. Others have found use for it in hypertension, psoriasis and in hematuria with kidney inflammation.

Folic acid

Foremost among the newer vitamin B complex factors is folic acid, or vitamin B_C. It occurs in green leaves and grasses and is therefore named from the Latin "folium", or leaf. It is also present in mushrooms and yeast and in liver and kidney. In rats, folic acid caused a marked increase in growth. An experimentally-developed leucopenia and dysentery in animals has been found to disappear when folic acid was administered.

Allergens and Viruses

The whole field of allergens and allergenic solutions must be dismissed with but a word. The present-day knowledge of allergy is such a small portion of the possible extent of this field that it represents, with the viruses, the world of research of tomorrow. There is no doubt that the viruses, as well as allergens, are proteins and it

is logical to suppose that from this basis research will develop tomorrow's therapy. Then many of the current therapeutic and dispensing practices in Pharmacy and Medicine of necessity will be revolutionized.

Hormones

In the field of endocrinology there is something new every day. Hormones are being prepared commercially by two methods: (1) chemical synthesis and (2) extraction from organs, tissues, or body fluids with subsequent concentration and purification. The latter method is the one most commonly employed in the preparation of many of the frequently prescribed hormones.

Some hormones, like thyroxin, and certain sex hormones, are active and have a demonstrable influence after either oral ingestion or parenteral administration; others, such as the pituitary hormones, must be administered parenterally for optimum effect.

One disadvantage of early hormone preparations was the short duration of their action, and another disadvantage was their low potency. The production of hormones in pure state and the synthesis of esters with prolonged action have largely overcome these difficulties.

The potency of hormone preparations is declared in a variety of units. At present, whenever an endocrine preparation is composed of the pure hormone itself or of equally pure hormonal derivatives, such as the esters, it is usually prescribed on a weight basis. The measurement of doses in terms of units is still, however, the more common practice in the case of the estrogenic hormones.

When hormone preparations were first introduced into therapeutics, they were used mainly in replacement therapy. Later, it was found that the indications for hormone therapy far exceeded the restricted field of glandular deficiencies.

To attempt to summarize the recent developments in this field would require more space than is available. Nevertheless, it is suggested that a review of the subject be made, as it is certain that in months to come hormones may gain a position of importance in Pharmacy and Medicine comparable to that now held by the vitamins.

Hexestrol and Octofollin

These compounds, two of the newest synthetic estrogenic substances, have been synthesized in the phenanthrene series and have

powerful estrogenic action which in some instances is superior to estradiol and stilbestrol. They are of tremendous value in disorders of the menopause, senile vaginitis and pruritis, suppression of lactation and other ovarian disorders.

To return to blood, however, two new agents have a significance in this field which is too great to ignore.

Heparin and Dicoumarin

In blood transfusions it is necessary to employ an anticoagulant. The most popular of this class of drugs has been sodium citrate. Within the past few years there has been discovered, heparin, a substance which occurs naturally in the body and is responsible for the blood remaining sufficiently liquid to circulate and oppose the bodies which tend to coagulate it.

Dicoumarin, another new anti-coagulant, is presented as a suitable replacement in certain conditions for heparin. The latter acts *in vitro* while dicoumarin acts in the human blood system. Heparin is of value particularly in hematuria, cerebral hemorrhage and hematoma, while dicoumarin is employed in various hemorrhages, purpura, epistaxis and ecchymoses.

Up to this moment, we have devoted our consideration to new agents. There are equally important developments in practice which deserve brief mention.

Ointment Bases

As far as newer practices go, we must select but one or two of the more striking ones for discussion. Pharmacists in the drug stores and hospitals of the nation are finding that a new world of opportunity is opening. Dispensing technics are of prime importance to all of us and among the newer agents and processes are improved ointment bases, stabilizing agents and emulsifying materials.

The following considerations are those which I regard as the most important in the formulation of an ointment base: (1) freedom from any tendency to rancidity; (2) type of base to be used; (3) suitability and compatibility with a variety of substances; (4) suitable pH; (5) ease of removal.

Dealing with the points in the order given, I think we may dismiss No. 1, since there is no excuse nowadays, considering the choice of material available, for producing an ointment with any tendency

to rancidity. No. 2 presents us with a choice of three types of base, (a) the oleaginous base with which we are already familiar; (b) the emulsified base, both w/o and o/w; and (c) the non-fatty base. These oleaginous bases have been used for years with questionable results. Their defects are that they do not permit the free liberation of the contained medicament; that in some cases they actually inhibit the therapeutic effect of the medicament; and that they are usually difficult to remove from the skin. The emulsified base presents us with a choice of either an o/w or a w/o emulsion. Which to choose is rather more difficult, but bearing in mind that an emulsion with water as the continuous phase is able to wet all kinds of skin and mucous surfaces, the o/w type seems to be preferable. Non-fatty bases are gradually becoming more popular.

When considering the suitability of a base, it is obvious that if it is to be of general application, it must be compatible with a variety of substances. It should also be borne in mind that a particular substance may not exhibit its full therapeutic effect in a particular base. Phenol, for example, a substance with high bactericidal power, loses this property entirely when compounded with soft paraffin, but retains it when presented in a vanishing cream base and to an almost equal extent in a cold cream base. With regard to pH, the usual requirement is for the base to be neutral or slightly acid. I believe that an effective nasal jelly should have a pH between 6 and 6.5, and that antiseptics as a class show greater activity in a neutral or slightly acid base.

Neglecting altogether the oleaginous base, the two most useful substances for producing non-fatty bases are bentonite and methyl cellulose. Bentonite and methyl cellulose are both colloids and are non-fermentable and do not become rancid. In addition, ointments prepared with bentonite possess the advantage of not spreading to the hair when applied to the scalp. Although methyl cellulose has not this property, it is an exceptionally useful substance. Bases prepared from these two substances keep well if evaporation of water is prevented.

For producing the emulsion types of base there is a large choice of material. Wool fat and its derivatives are still the leading bases so far as w/o emulsions are concerned, although there is now no excuse for producing a sticky ointment with wool fat as the chief ingredient. Wool wax is an improvement and there are also several lanolin absorption-bases consisting essentially of the water-absorbing fraction of

lanolin together with petroleum jelly. Cholesterol, cholesterol concentrates, cetyl and stearyl alcohols are also available.

Collyria

No dispensing technics have shown greater change than have those pertaining to ophthalmic preparations and therapy. The advent of physics into medicine, through employment of hydrogen ion concentration, buffering and isotonicity procedures renders the common empiric technic obsolete.

In the consideration of the proper method of preparation of collyria, two separate schools of thought are found. One group of workers interested in the field of ocular therapeutics advocates the adjustment of the acid and alkali value, or pH,—and the other lays stress on the tonicity. Most unbiased workers at present believe that both may be satisfactorily brought about in the same solutions in most instances.

For those who do not have clear in their minds just what these terms signify in their relation to one another let us quote the following: "Many of the compounds which are pharmacologically important are acids, bases or salts thereof. In aqueous or hydroalcoholic solution they tend, in great or small degree, to dissociate into their respective ions. The concentration and activity of hydrogen ions in a solution influences the concentrations of the anions, cations, and undissociated molecules present in the solution. These factors, in many instances affect the stability, therapeutic activity, and pharmaceutical elegance of medicaments in aqueous or hydroalcoholic solutions".

Hydrogen ion concentration is the number of positively charged hydrogen atoms which are present in a solution of an electrolyte (a substance which dissociates in solution). Because the numerical values of hydrogen ion concentration vary greatly, they are usually expressed in terms of the logarithm of the reciprocal which is denoted as the pH value.

pH is therefore a number denoting the degree of acidity or alkalinity of a solution. The pH scale runs from 1 to 14, a pH of 7 being neutrality, that is, neither acid nor alkaline. From 1 to 7 is the acid side, and 7 to 14 is the alkaline side.

As far as the preparation of collyria is concerned, it is desirable that these solutions be "buffered". When so "buffered", the

collyria are kept at a definite pH (predetermined degree of acidity or alkalinity).

To "buffer" is to add certain substances or solutions of those substances which may both provide and maintain a definitely desired pH, or they may only maintain the already existing pH value. For example, if it is desired to hold a reaction mixture or solution at a given pH value, this can be accomplished by adding a buffer which exerts buffer action and holds the medium at this pH. It is, of course, necessary to select in practice a buffer which will not interfere with the main reaction, and to make the concentration of the buffer salt such that it will neutralize the effect of any acid or alkaline materials that may be formed by the reaction.

When collyria are buffered at a desired pH, they are less irritating, more readily absorbed, and are more stable. For instance, it has been stated that certain drugs act better at an acid pH while others are more efficacious when administered in an alkaline pH medium. In general this may be summarized as:—Certain drugs act more effectively at a specific pH. In non-specific cases, the pH of lachrymal fluid should be used.

The pH of lachrymal fluid or tears is commonly accepted to be approximately 7.4, though some authorities state variations from 7.2 to 7.6. Still others maintain that the ocular secretion has a pH of 8.4-8.6 and recommend that collyria have a pH of 7.8, it being more desirable when nearer neutral than when more alkaline than the secretion. The solution to the question of the exact pH of lachrymal fluid is hampered by the difficulty in obtaining sufficient material, and by variations in "normal" individuals.

In general, conditions causing acidity in the eye should be treated with alkaline collyria and vice versa.

How to prepare the collyria and how to buffer them is the next question. By preparing stock solutions in advance of certain buffer solutions of known pH, and by mixing them in certain proportions as desired, certain intermediate pH values may be obtained.

The second school of thought in the field of collyria holds to the tonicity theory. When any solution is applied to the eye tissues, unless that solution is exactly in tonus with the lachrymal fluids commonly secreted as tears, a smarting or irritation occurs. Nearly all fluids from distilled water to a concentrated saline mixture may be expected to be hypo- or hypertonic unless specially adjusted.

These differences in tonicity are due to variations in the osmotic pressure produced by the drugs in solution. The osmotic pressure of a solution must be of the same value as that of the lachrymal fluid if the former is to be nonirritating. Discomfort, even pain, results when an eye solution has a different osmotic pressure than that of the fluids of the eye, and it continues until reaching equilibrium. This difference in pressure may be traced to the degree of concentration, to the difference in molecular weights of the contained salts, and to the dissociation of the same materials.

If the osmotic pressure of the collyrium is greater than that of the lachrymal fluid (the collyrium is therefore more concentrated and is hypertonic) there will be a tendency for fluids to pass out of the eye tissues causing a type of dehydration. When the osmotic pressure of the collyrium is lower than that of the lachrymal fluid (therefore hypotonic) there will be passage of more fluid into the eye until in either case equilibrium is established at that point where both osmotic pressures are the same.

It is therefore logical to conclude that in treating the eye it would be more efficacious to provide a solution equal in osmotic pressure (or isotonic) than to force the establishment of an equilibrium, a procedure both injurious and irritating to the eye.

Osmotic pressure, vapor pressure lowering, freezing point depression, and boiling point elevation caused by a substance in solution are referred to as the colligative properties of that substance. This means that these properties depend upon the number rather than the kind of particles present. It requires special apparatus and handling to determine osmotic pressure,—and it is more practical to determine the freezing point. The freezing point is directly proportional to the osmotic pressure, and the formula of a desired solution may easily be calculated when certain freezing points are known.

In the preparation of properly isotonic collyria, several methods may be found applicable. In general, the usual method of deriving isotonic solutions consists of adding such amount of a dissociating salt in addition to the active ingredient of the collyrium to give that solution the same osmotic pressure and the same freezing point as lachrymal fluid. Care must be taken in the selection of these added substances, using usually sodium chloride or boric acid, that they do not react with the active medicinal agent.

In a majority of cases in the preparation of collyria, boiled water is all that is necessary to satisfactorily preserve the lotion, but in such

preparations there is considerable possibility, and generally a probability, of reinfection from cork contamination. A wise precaution is to rinse the bottle with boiling water as well. If the collyrium is to be diluted before using, glycerin is sometimes suitable as a preservative. Not more than 6 to 8% is advisable, though up to 25% content is necessary for certainty in preservation.

The n-butyl parahydroxybenzoate has been found effective in preventing mold growth in ophthalmic solutions. Only one gram is necessary to adequately replace ten grams of benzoic acid. However, this ester is incompatible with zinc salts.

Sterilization of collyria is a necessity. A great many disease conditions in the eye are traceable to bacterial infection, and it is logical to suppose that it would be unwise to treat such conditions with medicinal agents contaminated with additional bacteria. In cases of physical injury to the eye, sterile collyria are positively indicated, for at such times the eye is more susceptible to infection.

Conclusion

After figuratively "hitting the high spots" of the newer developments in Pharmacy, one cannot help but appreciate that this is indeed a great period in the history of medical science. These few points illustrate only too well the indications of change and development referred to in our earlier remarks. Professional pharmacists may feel certain that the coming years hold for our practice a period of tremendous responsibility,— a challenge,—and an opportunity. Are you awake to it and are you preparing for it?

THIRD N. F. SUPPLEMENT WILL SOON BE AVAILABLE

Bound copies of the Third Supplement to N. F. VII, containing ten pages of new monographs and revisions, will soon be available to pharmacists, Justin L. Powers, chairman of the Committee on National Formulary, has announced. Propylene glycol, cinnamic aldehyde, eugenol and synthetic papaverine hydrochloride are among the drugs that now become official.

Research at the laboratory of the American Pharmaceutical Association and elsewhere has developed standards for propylene glycol, which serves as a replacement for glycerin. It has been authorized for use in twenty-eight N. F. preparations.

Preparations compounded with propylene glycol should be no less satisfactory than those made from previous formulas, Dr. Powers points out, although they will not have the same viscosity and body. The slightly acrid taste of propylene glycol is usually masked by other ingredients in a preparation, and improved methods of manufacture may eventually eliminate it entirely.

The replacement of oil of cinnamon by cinnamaldehyde and of oil of clove by eugenol have been authorized because of the shortage of spice drugs and certain essential oils. The N. F. admission of synthetic eugenol is reasonable since oil of clove distilled from the dried flower buds of the clove tree contains at least 82 per cent eugenol.

As imports of official arnica have nearly ceased, the Third Supplement gives official sanction to the use of closely related species which grow in our own west central states.

Since synthetic papaverine hydrochloride has been fully established as equivalent to its natural counterpart from Asiatic opium, the man-made product now becomes official. Due to shortages, it also becomes permissible to replace lactose, as a diluent for pepsin, by a mixture of sucrose and starch specified in the Supplement.

The complete supplement has been published in the Journal of the American Pharmaceutical Association (*Prac. Phar. Ed.*, 4:384) and bound copies will soon be available.

SELECTED ABSTRACTS

Sulfamerazine: Clinical Evaluation in 400 Cases. H. F. Flippin, J. G. Reinhold and W. I. Gefter. *M. Clin. North America 27,* 1447 (1943); through *U. S. Naval Med. Bull. 42,* 667 (1944). Sulfamerazine was used in the treatment of 400 patients with a variety of acute infections. The therapeutic results obtained with the drug in the cases of pneumococcal and meningococcal infections were comparable in all respects to those observed by the authors when sulfadiazine was used. In the other conditions in which sulfamerazine was used it appeared to be as effective as sulfadiazine, although the limited number of cases prevented a definite comparison.

Higher blood levels of drug are attained more rapidly and sustained longer by sulfamerazine than by sulfadiazine, a fact which makes it possible to maintain a given concentration in the blood with smaller doses of the former than of the latter. This feature may make sulfamerazine more valuable than sulfadiazine as a prophylactic agent. The rapidity with which sulfamerazine is absorbed frequently makes unnecessary the parenteral administration of the drug.

The toxicity of sulfamerazine was found to be no greater than that of sulfadiazine. Owing to the possibility that urinary complications may occur the routine use of alkalies is advisable.

Response of Acute Poliomyelitis to Large Doses of Plasma. G. L. Barnum and A. G. Bower. *U. S. Naval Med. Bull. 42,* 730 (1944). Eight consecutive acute cases of poliomyelitis occurring in the Hawaiian area were treated successfully by the administration of massive amounts (1,500-2,500 cc.) of dried plasma. In all cases the degree of infection was severe, but no residuals were observed following the course of treatment.

No convalescent pooled serum was available for administration to the first patient. It was thought that dried plasma might contain a sufficient number of antibodies to be of benefit if it were given

in large doses. Accordingly 1,250 cc. were given immediately, followed by 1,000 cc. later the same day. Improvement in the patient's condition was noted within twenty-four hours. Hot wet packs were then applied to the extremities. During the next few days two additional 500 cc. doses of plasma were administered. The patient returned to duty within a few weeks.

In this preliminary report the authors offer no explanation for the remarkable response to treatment, and state that further studies are in progress.

Skin Sensitization Produced by Local Applications of Sulfonamides. C. T. Bingham. *U. S. Naval Med. Bull. 42,* 680 (1944). The local application of sulfanilamide powder or sulfathiazole ointment to an open lesion may sensitize some patients either to further local application or subsequent oral administration of the sulfonamides. Reports are presented concerning the reactions exhibited by four patients who received such therapy.

(1) Sulfathiazole ointment was applied for six days to a fungus lesion of the foot which had resisted previous therapy with other remedies. A maculopapular eruption then appeared, necessitating other treatment for three weeks. The ingestion of 1 gm. of sulfathiazole by mouth about a month later led immediately to an acute generalized eruption which persisted for a week.

(2) Sulfanilamide powder was applied daily for 30 days to a case of dermatophytosis of the foot. The treatment resulted in a generalized eruption which was attended by complications requiring hospitalization for an additional month.

(3) A patient with a vesiculosquamous eruption of the thumb received local dusting treatment with a sulfonamide powder for a week, after which time potassium permanganate compresses were tried unsuccessfully for nine days. Three weeks later sulfathiazole ointment therapy was instituted, after four days of which a morbilliform eruption due to drug toxicity appeared, requiring hospitalization of the case for three more weeks.

(4) A case involving a minor skin infection resulting from a small burn was treated successfully by daily local applications of a sulfonamide powder for a month. After an additional month this

patient received applications of sulfathiazole ointment for three days and a dusting treatment with sulfanilamide powder for six days for a pustular lesion on the neck. Since he apparently tolerated the sulfonamides well, he received 2 gm. of sulfathiazole orally. Within three hours he became completely covered with a maculopapular rash, accompanied by acute malaise, pruritis, and an edematous swelling of the neck. This eruption, however, yielded within a week to treatment with boric acid compresses to the neck and calamine lotion to the rest of the body.

Acute Meningococcemia with Response to Sodium Sulfadiazine and Adrenal Cortex Extract Therapy. C. S. Greene. *Clinical Med. 51,* 42 (1944). The acute fulminating form of meningococcal septicemia, known as the Waterhouse-Friderichsen syndrome, usually occurs in infants and young children and ordinarily is fatal in less than twenty-four hours. Although the sulfonamides have been used previously in the treatment of meningococcemia, particularly in its chronic form, the case described in this paper constitutes the first report of the use of adrenal cortex extract in this disease and is remarkable because of the dramatic clinical response observed.

The patient, a four-year-old boy, became acutely ill within a few hours after the onset of symptoms. Sodium sulfadiazine, 1.59 grams in 5 per cent solution, was administered intravenously, followed by 250 cc. of citrated whole blood and 300 cc. of physiological saline solution. Shortly thereafter a 5 cc. dose of adrenal cortex extract was given intravenously and a similar dose intramuscularly.

Therapy was continued by the administration of two additional intramuscular doses of adrenal cortex extract, one intravenous injection of sodium sulfadiazine, and a course of sulfadiazine orally during six days. The patient was discharged on the eighth day.

No toxic effects of sulfadiazine were noted in the blood or urine, although the blood level of the drug reached 16 mg. per cent during the first twenty-four hours.

Demerol: Caution in Administration to Patients with Intracranial Lesions. S. A. Guttman. *J. A. M. A. 124,* 155 (1944). Demerol (the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid) was administered parenterally in the deltoid region to

twenty patients with intracranial lesions, usually in a dose of 100 mg. Morphine sulfate is considered to be contraindicated in such cases because of its depressant effect on respiration and the alteration in pupillary response.

Data including blood pressure, pulse and respiratory rate were obtained prior to the administration of demerol. Observations of its effects were made at intervals of fifteen minutes for about three hours thereafter, during which time all patients remained in bed.

Seven patients exhibited an unsafe respiratory depression after they received demerol; the premedication rate of 18 to 22 per minute fell to 12 per minute in five cases, to 8 per minute in one case, and to 4 per minute in one case. Abstracts on three of these patients are presented. Respiratory depression was much less pronounced in the remainder of the cases.

In this series of cases seven instances of contracted pupils with sluggish response to light were observed.

It is recommended that demerol should be administered with caution, if at all, to patients with intracranial lesions.

Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis. L. Loewe, P. Rosenblatt, H. J. Greene and M. Russell. *J. A. M. A. 124,* 144 (1944). Seven patients with subacute bacterial endocarditis were treated successfully by the administration of penicillin and heparin. The organism present was *Streptococcus viridans* in five cases, and *S. haemolyticus* and pneumococcus, type 27, respectively, in the other two. In six of these cases sulfonamide therapy was first tried and found ineffectual.

Penicillin was administered by the continuous intravenous drip method in all cases, although one patient also received the drug intramuscularly. Heparin was given subcutaneously in most instances in doses of 200 to 300 mg. on alternate days, although occasionally it was administered intravenously in combination with penicillin. In four cases a single course of treatment covering from thirteen to sixteen days proved adequate. In the remainder of the cases it was necessary to institute additional courses of treatment after it became apparent that a cure had not been effected.

The daily dosage of penicillin varied from 100,000 to 200,000 Florey units in most of the cases, the total amount administered

throughout the course of treatment varying from less than 900,000 units to nearly 8,000,000. The total amount of heparin administered varied from 1,200 mg. to 7,600 mg.

Post-therapy management included the removal of possible foci of infection by the extraction of diseased teeth in three cases and a tonsillectomy in one. These procedures were accompanied by local prophylactic therapy with penicillin.

The authors consider it possible that in a few cases the efficacy of the penicillin-heparin therapy may have been enhanced by the preliminary use of sulfonamides.

Pharmaceutical Preparations of Penicillin. H. W. Florey and H. Cairns. *Pharm. J. 98,* 28 (1944). The paper summarizes parts of a preliminary report to the War Office and the Medical Research Council in Great Britain on the use of penicillin under the direction of the authors in about 300 cases in the military campaigns in North Africa and Sicily. Owing to the limited quantity of the drug available, it was necessary to investigate the possibility of using locally smaller amounts of penicillin than would be administered intravenously or intramuscularly.

The drug was applied locally either in solution, as a dusting powder, or as a paste. Sterile aqueous or saline solutions of the calcium salt of a strength of 250 units per mil were found to be capable of controlling pyogenic cocci when instilled into wounds by means of small rubber tubes. Large volumes of the solution were found disadvantageous, since this tended to keep surfaces apart and thus interfered with normal healing.

For use as a powder, a mixture of pencillin and sulfanilamide was prepared by trituration, the concentration of the former being usually 500 units per gram, although in some cases the strength was raised to 5000. The mixture was applied to the infected area by means of an insufflator, but this method was believed to be wasteful and ineffectual, especially in the presence of profuse bleeding.

The paste contained 250 units of calcium penicillin per gram in a base prepared with 30 per cent Lanette wax SX. This was applied successfully as a dressing for infected burns and wounds.

For parenteral administration the sodium salt was used. Three mils of an aqueous solution containing 5000 units per mil were in-

jected intramuscularly every four hours. This mode of treatment, however, proved painful to the patients, and therefore continuous intravenous injections of the drug in glucose saline were employed. Two liters of a solution containing 100,000 units were given in 24 hours.

An average of 550,000 units per case was used in 36 patients with compound fractures. The consumption of the drug in wounds of the soft tissues was less than 50,000 units, and about 15,000 units in penetrating head wounds.

Certain severely infected wounds required as much as 1,650,000 units. Cases of gonorrhea which were resistant to sulfonamide treatment received twelve intramuscular doses of 15,000 units each in 48 hours.

Pyrogenic and thrombogenic reactions were frequently observed. The sodium salt showed little or no deterioration, but the calcium compound exhibited some loss in activity after aging from three to five months.

SOLID EXTRACTS

The shortage of beef has again focused attention on the horse as a potential source of meat. Only human prejudice is responsible for the almost unanimous objection to it as a foodstuff. It is much more like beef than either pork or mutton and very few persons can distinguish it from beef when roasted. Horse meat is usually a darker red color than beef and the fat is of an intense yellow or orange-yellow color quite unlike beef, pork or lamb. A chemical test for its identification has been published which depends upon the presence of significant amounts of linolenic acid which is determined as the hexabromide.

AJP

Evidence that glycerin is a good vehicle for incorporating sulfonamides is presented in the recent report by E. H. Wood, who is a Lieutenant Colonel in the Canadian Army Medical Corps. In an article in Clinical Medicine (50:231, 1943) *he says that after many trials it was found that 30% sulfathiazole in glycerin was generally the most satisfactory. The preparation, known as "sulfathiazole and Glycerin Cream 30%" is easily made by mixing the two components in a clean mortar with a clean pestle and a smooth cream results which is put into a clean jar. There is no apparent need to sterilize the mixture and the cream is said to have none of the disadvantages of other preparations. It is easily made, is chemically stable and it stands extremes of temperature well.*

The sulfathiazole-glycerin cream has a wide field of usefulness and has been employed in such varied conditions as: minor surgery and accidents, general surgery, leukorrhea, burns, osteomyelitis, tonsillectomy, pre-operative skin preparation and in compound fractures.

AJP

The need for fats is understandable when one realizes some of the uses to which they are put. In the synthetic rubber industry alone 100,000,000 pounds of soap are needed yearly for emulsification prior to polymerization. Thus the tires and spares for a 2½ ton army truck take 31 pounds of soap.

Caudal analgesic which was announced about a year ago as a technic for almost painless childbirth has recently been further endorsed inasmuch as it has been found to appreciably shorten the third stage of labor as well as reduce the amount of blood lost to a considerable degree. Since the third stage of labor is by far the most hazardous to the mother this is indeed a very real opportunity for improving childbirth technic. On the second point, hemorrhage was reduced from an average of 192 cc. of blood in ordinary technics to 110 cc. using caudal analgesia.

AJP

To relieve the current critical paper shortage, there has been developed for Army Ordnance a quick, simple dip-coating method utilizing an ethylcellulose plastic compound. Delicate machine parts which would ordinarily require grease coating and two or three layers of moisture-proof paper to protect them during shipment, may now be dipped into this plastic coating and, in less than a second, acquire a covering that will resist corrosion and rough handling. At the other end, the coating may be split with a knife and peeled off like a banana skin.

Other new and unusual uses for plastics include shoe soles that are claimed to be better in every way than those made of leather, replicas of guns to be used in training soldiers, luminous paints, transparent pill boxes for soldiers' sulfadiazine tablets, and laminated transparent window sheets containing wire.

AJP

A letter from one of our readers gives us an interesting translation of a preparation from a Russian Physician's Manual written by M. X. Bergolitz, Moscow, 1942. This preparation called "Aeron" is intended as a remedy for sea-sickness or air-sickness and it has the following composition: hyoscyamine camphorate 0.0004 gm. and scopolamine camphorate 0.0001 gm. per tablet. It is taken prophylactically in two (2) tablet doses one hour before flight or at the appearance of the first symptoms of sea-sickness. Not more than four tablets should be taken in 24 hours.

BOOK REVIEWS

Organic Chemistry Simplified. Rudolph Macy, Chemist, Chemical Warfare Service, formerly Assistant Professor of Chemistry, University of Maine. Chemical Publishing Company, Inc., Brooklyn, New York, 1943. viii + 431 pages, 15 x 23 cm. $3.75.

This book is intended for those just beginning the study of organic chemistry and also for those who wish to refresh their memory of the organic chemistry studied a number of years ago. The book offers simplified explanations of the newer terms such as resonance, dipole moment, etc., but is weak on the usual organic chemistry found in a standard text-book. It is suggested by the author that such things be found in larger books.

"Organic Chemistry Simplified" is divided into four general parts. Part I, entitled "The Unique Position of the Atom in Chemistry," deals with valence, the periodic system, dipole moments and dielectric constants.

Part II—"The Architecture of Carbon Compounds" discusses methane and related compounds, cycloparaffins including the Baeyer strain theory, double and triple bonded compounds and their properties, stereochemistry and isomerism, resonance, conjugate systems, the structure of the benzene ring and orientation.

Part III—"The Classification of Carbon Compounds" includes open chain and ring compounds, halogen compounds, alcohols, phenols, ethers, aldehydes and ketones, acids, polyfunctional compounds, nitrogen compounds and compounds of sulfur, phosphorus and arsenic.

Part IV—"Special Topics in Organic Chemistry" deals with heterocyclic compounds, isoprene compounds, proteins, carbohydrates, dyes, drugs, hormones and vitamins, isotopic chemistry and giant molecules.

The following comments and criticisms are offered. The statement (p. 195), "Most of the halogen compounds used for synthetic work in the laboratory are those containing iodine, because of the greater reactivity of the iodine compounds" is subject to question in

regard to the use of iodine compounds in synthesis. Use of the general formula Ar. X to illustrate both benzyl chloride and *o*-chlorotoluene (p. 197) appears to be a poor choice. The chlorination of benzoic acid (p. 249) is illustrated by the formulation of the *o*- and *p*-chlorobenzoic acids. The naming of acetonitrile (p. 296) as methylnitrile is not very good nomenclature. In considering the α- and β-cyclic forms of fructose and glucose (p. 346) the statement is made that "these cyclic forms of the sugars are not optical isomers." The α- and β-forms of fructose or of glucose are diastereoisomers and therefore optical isomers. In the equations illustrating the formation of d-glucosazone it would probably be better to include the step in which the d-glucose phenylhydrazone is oxidized.

The book is easy to read and would appeal to the reader who is interested in a simplified explanation of some of the theoretical concepts of organic chemistry.

N. RUBIN.

Synopsis of Materia Medica, Toxicology, and Pharmacology. By Forrest Ramon Davison, B. A., M. Sc., Ph. D., M. B. Third Edition. C. V. Mosby Co., St. Louis, Mo., 1944. 759 pp. Illustrated. Price: $6.50.

In this volume is presented as briefly as is consistent with thoroughness, the information about drugs essential for the medical student, practicing physician and of value to the pharmacist.

Emphasis is placed on those drugs most commonly used but the more promising new drugs are also included. There is an extensive monograph on penicillin, the new microbiotic agent.

The book, in this third edition, has been completely revised.

The author first presents the basic principles of pharmacology, materia medica and toxicology and then presents the essential facts on the individual drugs according to their classification.

Each monograph is succinctly but clearly written and includes suggestions for the actual writing of the prescription for that particular drug in the indicated conditions.

Although written for the medical man the pharmacist will find the book of great value as a reference.

M. O. H.

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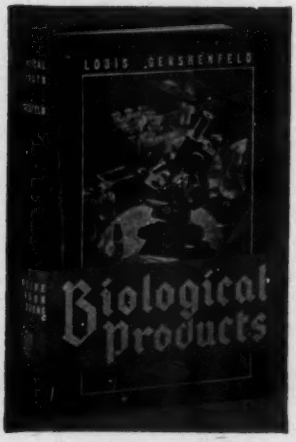

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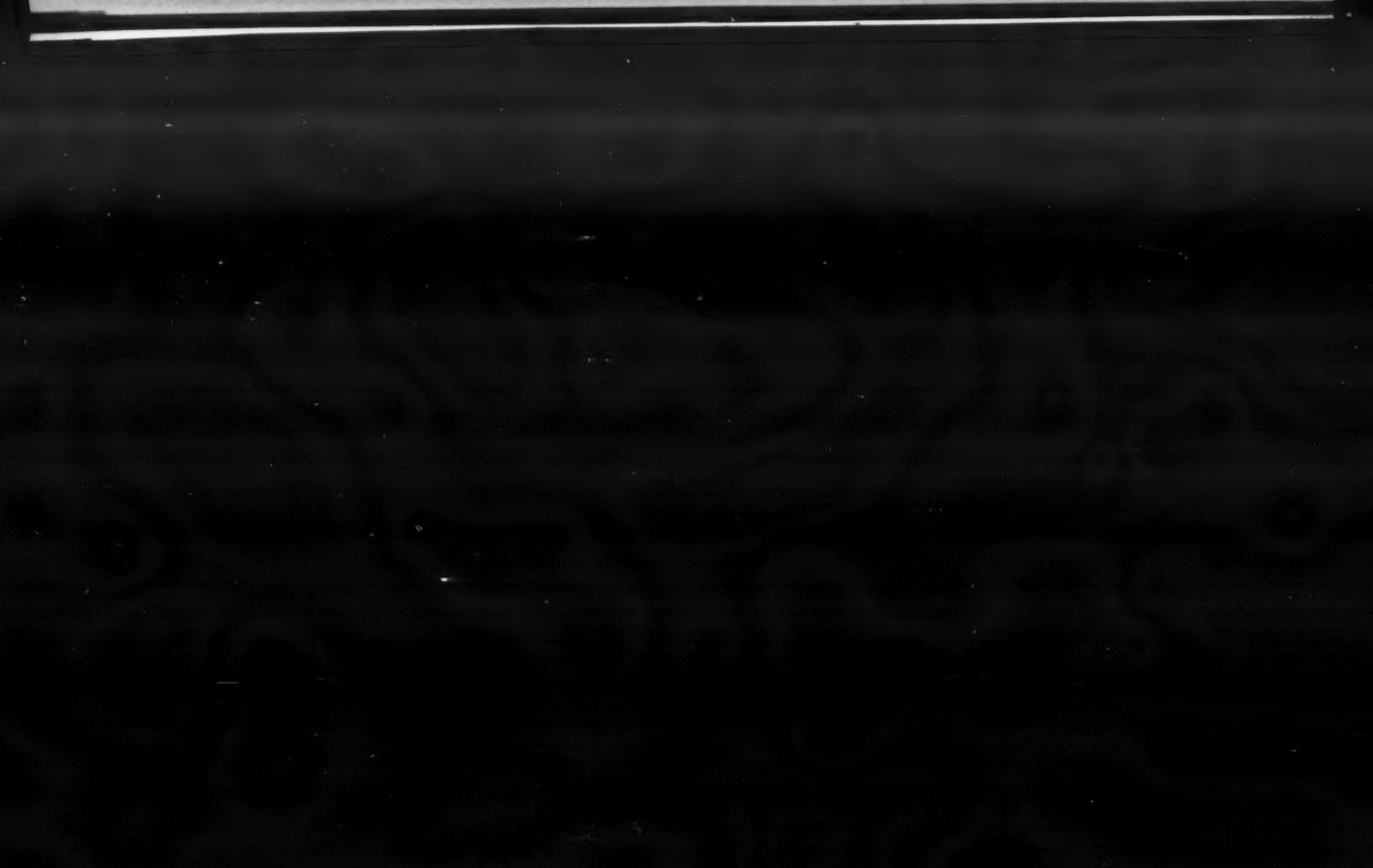

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